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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	25

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/359,593	GARVER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-19,21-26,28-40 and 42-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,10-19,21-26,28-40 and 42-50* is/are rejected.

7)☒ Claim(s) *8 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/01/03 has been entered.

Amended claims 1, 4-19, 21-26, 28-40 and 42-50 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 15, 17-19, 22, 30-32, 34, 39 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new ground of rejection necessitated by Applicants' amendment.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction

or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1, 4, 15, 17-19 and 22 are drawn to a composition for controlled release of a nucleic acid of the present invention, wherein the microsphere when administered to a host, provides controlled release of an expression vector. Claim 39 is directed to a method for preparing a pharmaceutical preparation, comprising combining a pharmaceutically acceptable excipient with a coacervate of cationic and anionic molecules, wherein a recombinant virus is encapsulated in said coacervate.

Claims 30-32 and 34 are directed to a method for delivering a nucleic acid into a cell comprising contacting a cell with a composition comprising a coacervate having limitations recited in claims 30 and 31, wherein the nucleic acid encodes a bioactive protein, the cell is in a host and is transfected with the nucleic acid and express the bioactive protein, or wherein the coacervate microsphere is administered to a host as a pharmaceutical composition. Claim 50 is directed to a method for the sustained release of a virus to a cancer cell, comprising providing to the target site a coacervate microsphere comprising a coacervate microsphere of gelatin and alginate having a virus incorporated therein.

The specification teaches by exemplification showing the preparation of microspheres made by the coacervation of gelatin and alginate in the presence of a recombinant adenovirus containing a luciferase expression cassette. Lyophilization of a

recombinant adenovirus within a microsphere of the present invention was also shown to minimize the bioactive loss in comparison to the lyophilization of free adenovirus. Using a human lung cancer engrafted on nude mouse model, it was demonstrated that bioactive adenovirus was released *in vivo* from the microspheres that were injected intratumorally, as evidenced by the luciferase activity in harvested tumor nodules. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instantly claimed invention for the following reasons.

When read in light of the specification, with respect to claims 1, 4, 15, 17-19 and 22, the only purpose for administering the composition of claim 15 into a host for controlled release of an expression vector or for the preparation of a pharmaceutical preparation is intended for obtaining therapeutic effects. It should also be noted that enablement requires the specification to teach how to make and **use** the claimed invention. With respect to claims 30-32, 34 and 50 are drawn to methods for delivering a nucleic acid or a virus in the form of a coacervate to a cell in a host or a cancer cell and for preparing a pharmaceutical composition comprising a coacervate of the present invention containing a recombinant virus for the sole purpose of gene therapy and/or nucleic acid immunization or for obtaining therapeutic effects in general (See page 3 of the specification, lines 1-5 and 17-19).

(a) The breadth of the claims. The instant claims encompass a composition for controlled release of a nucleic acid in the form of a coacervate microsphere of the present invention, wherein the microsphere when administered to a host, provides controlled release of any expression vector, as well as a method for preparing any

pharmaceutical preparation, comprising combining a pharmaceutically acceptable excipient with a coacervate of cationic and anionic molecules, wherein any recombinant virus is encapsulated in said coacervate. Additionally, the claims also encompass methods for delivering any nucleic acid into any cell comprising contacting (by any route of delivery at any site) a cell with a composition comprising a coacervate having limitations recited in claims 30 and 31, wherein the nucleic acid encodes any bioactive protein (defined by the instant specification as any substance that will produce a therapeutically beneficial response when administered into a host, see top of page 7), the cell is in any host and is transfected with the nucleic acid and express the bioactive protein, or wherein the coacervate microsphere is administered to a host as a pharmaceutical composition, as well as a method for the sustained release of any virus to a cancer cell, comprising providing to the cancer cell by any route of delivery at any site a coacervate microsphere comprising a coacervate microsphere of gelatin and alginate having a virus incorporated therein.

(b) The state and the unpredictability of the art. At the effective filing date of the present application, the art of gene therapy was still unpredictable with respect to the attainment of therapeutic and/or prophylactic effects. This is supported by numerous teachings in the art, such as Dang et al. (Clin. Cancer Res. 5:471-474, 1999, Cited previously), Verma et al. (Nature 389:239-242, 1997; Cited previously), Chattergoon et al. (FASEB J. 11:753-763, 1997; Cited previously), Leitner et al. (Vaccine 18:765-777, 2000; Cited previously), McCluskie et al. (Mol. Med. 5:287-300, 1999; Cited previously).

(c) The amount of direction or guidance presented. The specification is not enabled for the claimed invention because it fails to provide guidance for one skilled in the art on how to make and use the claimed methods and compositions to obtain any therapeutic effect contemplated by Applicants to treat a plethora of diseases, disorders or genetic defects such as Duchenne and Becker muscular dystrophy, adenosine deaminase deficiency, cancer, Parkinson's, Alzheimer's, AIDS among many others (specification, pages 39-41). There is no specific guidance as to promoters, vectors or dosages that are utilized to treat a particular disease, disorder or a genetic defect. Moreover, there is no correlation between the luciferase activity detected in harvested tumor nodules that had been treated with coacervate microspheres containing recombinant adenoviruses of this invention with the therapeutic results expected for the treatment of aforementioned diseases, disorders and genetic defects. As the art does not teach such a correlation nor provide such guidance, it is incumbent upon the specification to do so. Additionally, at the effective filing date of the present application, gene therapy was still considered to be immature and highly unpredictable. Given the lack of guidance or direction provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

As noted in the previous Office Actions that there are several factors limiting an effective gene therapy, and these include sub-optimal vectors, the lack of a stable *in vivo* transgene expression, and most importantly an efficient gene delivery to target cells or tissues. The specification fails to provide teachings showing that a gene construct in the coacervate microsphere of the instant invention could provide an

efficient therapeutic transgene expression in targeted cells or tissues that results in desirable treatment outcomes for any diseases contemplated Applicants. Wivel and Wilson (cited previously) noted that an efficient gene therapy vector has not existed, and regarding the failure of the instant specification to provide guidance for a skilled artisan on how to make and use an efficient gene therapy vector other than those already known in the art, it would have required undue experimentation for one skilled in the art to practice the instant claimed invention.

The claims also encompass the utilization of a nucleic acid encoding any bioactive protein to be incorporated in the coacervate microspheres to treat aforementioned diseases, disorders and genetic defects. However, the specification fails to address issues such as the fate of delivering recombinant gene transfer vectors, the fraction of vectors taken up by targeted cells once they are released from coacervate microspheres, the level of mRNA produced, the stability of the recombinant protein produced, the recombinant protein's compartmentalization and its bioactive activity. These factors differ dramatically based on which recombinant protein being produced to treat which disease or disorder, and the desired therapeutic effect being sought. Therefore, the level of gene expression, its duration and its *in vivo* therapeutic effects are not always predictable, and they could not be overcome with routine experimentation. With the lack of guidance and direction provided by the specification, it would have required undue experimentation for a skilled artisan to make and use the instant invention.

Regarding to the deliverance of a transgene encoding any bioactive protein to a target cell in a host via coacervate microspheres, the specification fails to provide sufficient guidance or teachings on vector targeting to specific tissues or cells in the host. At the effective filing, vector targeting *in vivo* to desired cells, tissues or organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller & Vile (FASEB 9:190-199, 1995; Cited previously) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998; Cited previously) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation that show promise, but are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (Nature 389:239-242,1997; Cited previously) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at about the time of the claimed invention resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting the efficient targeting

of viral vectors such that an efficient transgene expression has not been achieved (see page 239, and second and third columns of page 242). Verma et al. also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). The specification fails to provide sufficient guidance for a skilled artisan on how to overcome the unpredictability of vector targeting *in vivo*, such that an efficient gene transfer and expression could be achieved in specific target cells via coacervate microspheres in order to attain the desired therapeutic results.

Furthermore, the instant specification fails to provide any guidance for a skilled artisan on how to use a sustained release of any virus in the form of a coacervate to a cancer cell, particularly one that expresses a luciferase activity in the exemplification and it is used as a support for the newly added claim 50. Would any virus have any effect on a cancer cell, and therefore does it have anything to do with therapeutic effects contemplated by Applicants? On the contrary, it is noted that certain cancers are caused by the infection of certain viruses, such as leukemia, cervix cancers. With the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Additionally, it should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). With regard to the breadth of the instant claims, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of gene therapy art for attaining therapeutic effects and/or prophylactic effects, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on July 01, 2003 in Paper No. 24 (page 8) have been fully considered, but they are not found persuasive.

Applicants argue that the specification provides adequate support for the delivery of a bioactive adenovirus encoding a bioactive protein to target cells and tissues in a host via coacervate microspheres, and the successful expression of a bioactive protein in target cells and tissues in a host, and therefore the amended claims conform fully with the scope of disclosure in the application. Additionally, Applicants argue that the

amended claims now recite "host" in lieu of "patient" and "bioactive protein" in lieu of "therapeutic agent", and therefore they should overcome the rejection under 112, 1st paragraph.

It is noted that a host encompasses a patient, and that a bioactive protein encompasses a therapeutic agent (see the definition of the term in the specification on page 7), particularly, when read in light of the specification the only purpose for administering the composition of claim 15 into a host for controlled release of an expression vector or for the preparation of a pharmaceutical preparation or for delivering a nucleic acid or a virus in the form of a coacervate to a cell in a host or a cancer cell and for preparing a pharmaceutical composition comprising a coacervate of the present invention containing a recombinant virus is intended for obtaining therapeutic and/or prophylactic effects.

Furthermore, there is no correlation between the luciferase activity detected in harvested tumor nodules that had been treated with coacervate microspheres containing recombinant adenoviruses of this invention in the sole exemplification with any therapeutic and/or prophylactic results for the treatment of a plethora ofdiseases, disorders and genetic defects contemplated by Applicants for the reasons set forth above, particularly when all of the *re Wands* factors have been taken into consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-26, 28 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new ground of rejection necessitated by Applicants' amendment.

Claim 24 and its dependent claims recite the limitation "said a viral vector" in line 2 of claim 24. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any viral vector in claim 1 on which claim 24 is dependent. Therefore, the metes and bounds of the claims are not clearly determined.

Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is the step of preparing the microspheres for administration to a host. How are the microspheres prepared for administration to a host? The metes and bounds of the claim are not clearly determined.

Claim 50 recites the limitation "the target site" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the

applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10-12 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Russell-Jones et al. (U.S. Patent No. 6,159,502). This is a new ground of rejection.

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate microsphere, (b) a nucleic acid incorporated in said coacervate microsphere, and (c) a delivery agent incorporated in said coacervate microsphere, wherein the coacervate comprises a polycationic molecule and a polyanionic molecule other than said nucleic acid and the delivery agent is other than said polycatonic molecule of the coacervate microsphere; the same composition wherein said coacervate is a microsphere or wherein said polyanionic molecule is alginate and said polycationic molecule is gelatin, and a gene delivery system comprising the same.

Russell-Jones et al. disclose the preparation for complexes and compositions for oral delivery of a substance or substances to the circulation or lymphatic drainage system of a host. The complexes comprise a microparticle or microsphere coupled to at least one carrier (e.g., mucosal binding proteins, bacterial adhesions, viral adhesions, lectins, Vitamin B12), the carrier being capable of enabling the complex to be transported to the circulation or lymphatic drainage system via the mucosal epithelium of the host, and the microparticle or microsphere being capable of encapsulating the substances (See abstract). Russell-Jones et al. teach specifically that the microsphere

can be made by complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims). As the term "delivery agent" is defined in the present application as a molecule that facilitates the intracellular delivery of a bioactive molecule, and examples of delivery agents include, sterols, lipids, viruses, target cell specific binding agents (page 9, second paragraph), the carrier molecule coupled to the microsphere of Russell-Jones would be qualified as a delivery agent (e.g., bacterial adhesions, viral adhesin, plant lectins are natural mucosal binding proteins that target various haptens and protein molecules to the gastrointestinal mucosa and elicit their uptake, col. 3, lines 30-35). Moreover, Russell-Jones et al. specifically teach that other molecules such as targeting molecules which target and attaché the complex to or in the vicinity of a desirable target in the host can be coupled to the microsphere, and these include antibodies, lectins, enzymes (col. 5, lines 26-38).

Therefore, the composition taught by Russell-Jones meets every limitation recited in the instant claims, and thus the reference anticipates the instant claims.

Claims 1, 7, 11, 29, 40 and 42-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Spence et al. (U.S. Patent No. 4,325,937). This is a new ground of rejection.

Spence et al. teach a microbial insecticide composition comprising : (a) a microbial insect pathogen of viral (e.g., Douglas fir tussock moth NPV viruses, Autographa californica NPV viruses, T-4 bacterial phages), bacterial, or fungal origin, (b) a coacervate microbead in spherical form which is comprised of a nucleic acid, typically RNA, and a proteinaceous material (e.g., gelatin, protamine, cytochrome c), whereby the microbead structure itself effectively shields the pathogen from sunlight-induced inactivation and that the microbead is typically stabilized by chemical crosslinking (see Summary of the Invention, cols. 2-3, examples 6, 9, 11). Spence et al. teach also a method for preparing the same composition, comprising: (a) preparing an queous solution containing a nucleic acid (a polyanion); (b) preparaing an queous solution containing a proteinaceous material; (c) preparing an aqueous suspension of strongly positively or negatively surface-charged microbial insect pathogens; and (d) mixing the aqueous solutions and suspension prepared in steps (a), (b), and (c) together, thereby spontaneously forming microbeads having the insect pathogens embedded therein, or in a preferred embodiment the suspension prepared in step (c) is first mixed with the solution prepared in step (a), and then this mixture is mixed with the solution prepared in step (b), or in a preferred embodiment the suspension prepared in step (c) is first mixed with the solution prepared in step (b), and then this mixture is mixed with the solution prepared in step (a) (col. 3, lines 52-68). As the coat protein of the microbial insect viral pathogen falls within the definition of the term "delivery agent" of the instant invention, and it should also be noted that nucleic acid of the microbial insect viral pathogen is not the same nucleic acid used for forming the coacervate, the

composition of Spence et al. meets every limitation of the instant claims, and therefore the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-6, 13-19, 23-26, 28, 30-31, 33-39 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997; Cited previously). This is a new ground of rejection necessitated by Applicants' amendment.

With respect to the composition claims 17-19, the intended use of the composition is not given any patentable weight in view of the prior art. With respect to

claims 34 and 39, the pharmaceutical composition or preparation is interpreted as a composition or preparation containing a pharmaceutically acceptable excipient, and not for the intended pharmaceutical use.

Within the enabled scope of the instant claimed invention, Russell-Jones et al. disclose the preparation for complexes and compositions for oral delivery of a substance or substances to the circulation or lymphatic drainage system of a host. The complexes comprise a microparticle or microsphere coupled to at least one carrier (e.g., mucosal binding proteins, bacterial adhesions, viral adhesions, lectins, Vitamin B12), the carrier being capable of enabling the complex to be transported to the circulation or lymphatic drainage system via the mucosal epithelium of the host, and the microparticle or microsphere being capable of encapsulating the substances (See abstract). Russell-Jones et al. teach specifically that the microsphere can be made by complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). It is also noted that Russell-Jones et al. also teach that other polymers that are suitable for formation of microspheres by solvent evaporation include amongst others, Poly-(Lactide/co-glycolide), poly-lactic acid, polyhydroxybutyrate (col. 9, lines 50-50-57). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims). Russell-Jones et al. also teach that the microspheres have size from 1 nanometer to 100 micrometers in diameters, and they can be prepared by a number of well known methods apart from the complex coacervation for encapsulation a desired substance,

(col. 2 and col. 4, lines 39-42). Additionally, the disclosed complex or composition can be mixed with a pharmaceutically acceptable carrier, diluent, excipient and or adjuvant (col. 14, lines 7-14). Russell-Jones et al. also teach a method of orally delivering a substance, such as DNA, RNA or ribozymes to the circulation or lymphatic drainage system of a host by orally administering to the host the complex comprising the microsphere and wherein the substance is released from the microsphere when the complex enters the circulation or lymphatic drainage system of a host (See examples 13, 14 and the claims). Additionally, Russell-Jones et al. also disclose a kit comprising a plurality of different carriers and a plurality of different microparticles or microspheres containing the same or different substance of interest to prepare a complex for oral delivery (col. 6, lines 64-67). As the term "delivery agent" is defined in the present application as a molecule that facilitates the intracellular delivery of a bioactive molecule, and examples of delivery agents include, sterols, lipids, viruses, target cell specific binding agents (page 9, second paragraph), the carrier molecule coupled to the microsphere of Russell-Jones would be qualified as a delivery agent (e.g., bacterial adhesions, viral adhesin, plant lectins are natural mucosal binding proteins that target various haptens and protein molecules to the gastrointestinal mucosa and elicit their uptake, col. 3, lines 30-35). Moreover, Russell-Jones et al. specifically teach that other molecules such as targeting molecules which target and attaché the complex to or in the vicinity of a desirable target in the host can be coupled to the microsphere, and these include antibodies, lectins, enzymes (col. 5, lines 26-38)

However, Russell-Jones et al. do not specifically teach the encapsulated DNA is in the form of a recombinant viral vector, wherein the nucleic acid is a viral vector and the delivery agent is a virus of said viral vector.

At the effective filing date of the present application, Beer et al. already disclose a composition of Poly(lactic-glycolic) acid (PLGA) microspheres containing a recombinant adenovirus, AdRSVntlacZ. Upon injection into the striatum of mice with microspheres containing AdRSVntlacZ, beta-galactosidase activity was detected in harvested brains after 7 days, and a dose dependent increase in beta-galactosidase activity was also noted (see Fig. 4). Although viable virus could be delivered both *in vitro* and *in vivo* from the PLGA microspheres, optimal microencapsulation yield, virus stability, and efficient transfer remained elusive (second column, second paragraph, page 63). Beer et al. suggested that different polymers should be investigated for their ability to allow for sustained release of recombinant viral vectors (column 2, last paragraph, page 63).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan at the time of the present invention was made to encapsulate the recombinant adenoviral virus into a microsphere composition taught by Russell-Jones et al. in light of the teachings of Beer et al. because a recombinant adenoviral virus has already been encapsulated into a microsphere for gene delivery.

One of ordinary skilled artisan would have been motivated to carry out such modification to improve the microencapsulation yield and virus stability in a microsphere in order to improve the efficiency of gene delivery (Beer et al., page 63, column 2, first

full paragraph), particularly an ordinary skilled artisan contemplates for a composition suitable for oral delivery of a substance to the circulation or lymphatic drainage system of a host as one taught by Russell-Jones et al. Beer et al. suggested that other methods and different polymers should be investigated for their ability to allow sustained release of recombinant viral vectors (column 2, last paragraph, page 63). A kit comprising the modified microsphere resulting from the combined teachings of Russell-Jones et al. and Beer et al. would have been obvious, as well as a method for delivering a nucleic acid to a cell using the modified microsphere. With respect to claim 16 reciting the incorporated virus comprising at least about five percent by weight of the microsphere, this would have been within the scope of skills of an ordinary artisan at the time of the instant invention to prepare the modified microsphere having such limitation. It is further noted that this is not the novel aspect of the present invention.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on July 01, 2003 in Paper No. 24 (pages 9-12) have been fully considered, but they are not found persuasive.

Applicants argue mainly that the microparticles of Russell-Jones et al. rely on the use of a carrier, and are delivered systemically to the host, whereas the instant amended claims lack any element which corresponds to the carrier of Russell-Jones.

Applicants further argue that the Russell-Jones reference fails to motivate or suggest to the skilled person that the disclosed microparticles should be modified by omission of the carrier molecule, nor does the Beer reference provide such motivation or suggestion. Additionally, the Beer reference fails to teach or suggest that coacervate microspheres in particular should be evaluated as potential encapsulation systems for viral or other nucleic acid vectors, and that Beer et al. injected microsphere preparation directly into the striata of mice in contrast to the Russell-Jones technique of oral administration for systemic uptake into the circulation and/or lymphatic drainage system of a host. Therefore, the combinations of these references do not render the instant claims obvious.

Applicants' arguments are found unpersuasive for the following reasons. Firstly, because the term "comprising" recited in the claims does not preclude other elements including the carrier of Russell-Jones to be incorporated into the microparticles, particularly Applicants also contemplate the coacervates to be administered orally (see specification, page 32, lines 15-17). Secondly, the claims do not limit that the coacervates have to be administered either locally or systemically. Thirdly, one of ordinary skilled artisan would have been motivated to carry out the aforementioned modification to improve the microencapsulation yield and virus stability in the microsphere composition of Beer et al. in order to improve the efficiency of gene delivery (Beer et al., page 63, column 2, first full paragraph), particularly if an ordinary skilled artisan contemplates for a composition suitable for oral delivery of a substance to the circulation or lymphatic drainage system of a host, and that a recombinant

adenoviral virus has already been encapsulated into a PGLA microsphere for gene delivery. Beer et al. suggested that other methods and different polymers should be investigated for their ability to allow sustained release of recombinant viral vectors (column 2, last paragraph, page 63). Russell-Jones et al. already note that the formation of microspheres through the coacervation process or the utilization of other polymers including the PGLA through solvent evaporation or other polymers through interfacial precipitation/polymerization for encapsulating the desired substance are well known methods in the art.

Claims 1, 7, 21, 40, 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997; Cited previously) as applied to claims 1, 4-6, 13-19, 23-26, 28, 30-31, 33-39 and 48 above, and further in view of Leong et al. (U.S. Patent No. 5,759,582, PTO-1449 # 6, AB). This is a new ground of rejection.

The teachings of Russell-Jones et al. and Beer et al. and the motivation for their combined teachings have been presented above. Neither references specifically discloses method steps for preparing the modified microsphere encapsulating a recombinant adenvirus resulting from the combined teachings of Russell-Jones et al. and Beer et al., or the microsphere is lyophilized or the microsphere is crosslinked by a crosslinking agent. Although Russell-Jones et al. teach that DNA or RNA or ribozyme can be encapsulated in a microsphere prepared by complex coacervation between mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose among

others with polycations of polylysine and gelatin (col. 10, lines 16-22 and the claims), they do not specifically disclose the method steps, because the process of forming a microsphere prepared from a complex coacervation is well known.

At the effective filing date of the present application, Leong et al. (US Patent No. 5,759,582) already teach a method for preparing a pharmaceutical composition in the form of a coacervate microsphere, comprising the following steps: (a) providing a gelatin (a cationic molecule) aqueous solution; (b) providing a chondroitin sulfate (an anionic molecule) aqueous solution; (c) adding a therapeutically effective amount of a pharmaceutically active substance either to the solution in step (a) or to the solution in step (b); (d) mixing the gelatin and chondroitin sulfate solutions to form a coacervate suspension; (e) adding a crosslinking agent to the coacervate suspension to crosslink the coacervates, the coacervates encapsulating the pharmaceutically active substance; and (f) incubating the coacervate suspension to form microspheres and recovering the microspheres. (col. 2 in summary of invention). Leong et al. further teach that after recovering the microspheres, they may be washed and dried in a standard techniques, e.g., lyophilization (col. 4, last paragraph).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to carry out the method steps for preparing a modified coarcevate microsphere taught by Russell-Jones et al. and Beer et al. similar to those disclosed by Leong et al. (US Patent No. 5,759,582) by substituting a pharmaceutical composition comprising water soluble protein, peptide, glycoprotein, or mixture thereof in step (c) with a recombinant adenovirus in order to obtain the modified microsphere

that encapsulates a recombinant adenovirus because the essential steps for preparing a coacervate microsphere are essentially the same in principles. The motivation for one of ordinary skilled artisan to carry out the modification with particular to the content of the modified coacervate microsphere is already discussed in the rejection of claims 1, 4-6, 13-19, 22-26, 28, 30-31, 33-39 and 48 above.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on July 01, 2003 in Paper No. 24 (page 12) have been fully considered, but they are not found persuasive.

Applicants argue mainly that nucleic acids in general are not present in a detailed list of substances considered to be pharmaceutically active substances in Leong reference, nor does it teach or suggest any molecular component for use as a delivery agent to target the microspheres or for providing any incentive, motivation or guidance for omitting a carrier molecule of Russell-Jones.

Applicants' arguments are respectfully found to be unpersuasive for essentially for the same reasons given in the Response for the rejection of 1, 4-6, 13-19, 23-26, 28, 30-31, 33-39 and 48 above. Furthermore, it should be noted this is a 103 rejection and therefore, the Leong reference does not have to teach every limitation of the claims.

Claims 1, 4-6, 13-19, 22, 30 and 49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO 94/23738, PTO-1449#6, AK). This is a new ground of rejection.

With respect to composition claims 17-19 and 22, the intended use of the composition is not given any patentable weight in view of the prior art.

The teachings of Russell-Jones et al. have been presented above. However, Russell-Jones et al. do not specifically teach that the encapsulated DNA is in the form of a recombinant transfer vector, or the encapsulated DNA is associated with any delivery agent or that the disclosed microsphere comprises a second expression vector.

At the effective filing date of the present application, McElligott et al. already teach that DNA or RNA molecules can be conjugated by way of chemical bonds with promoting material which promotes the uptake or the transport to the nucleus of cells, such as fatty acids, phospholipids, glycolipids among others (Summary of the invention), and that the conjugated genetic material can be encapsulated in a microsphere suitable for the controlled release of the nucleic acid molecule to a target cell (Summary of the invention). The microsphere can be prepared by various methods available in the art (pages 15-26). McElligott et al. further teach that encapsulation of genetic material would protect the nucleotides from enzymatic degradation before they are released, and that controlled release of genes would also reduce lethality to the host by allowing controlled expression of the product (page 4, lines 3-7). Specifically, McElligott et al. disclosed various plasmid expression vectors having a promoter, regulatory region along with the coding region of specific nucleotide sequence encoding

for the desired gene product, including cytokines or gene product killing cancer cells (page 9, lines 20-24; page 28, col. 20-22 and examples 1, 5).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to incorporate DNA in the form of a plasmid expression vector conjugate as taught by McElligott et al. into the microsphere composition disclosed by Russell-Jones et al.

One of ordinary skilled in the art would have been motivated to carry out the above modification, because the DNA in the form of a conjugate facilitates the uptake and integration of the genetic material into cells upon being released from the microsphere as taught by McElligott et al. With respect to claim 22 reciting further comprising a second expression vector, it would have been obvious for an investigator to have two or more different expression vectors being encapsulated into the same microsphere.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on July 01, 2003 in Paper No. 24 (page 12) have been fully considered, but they are not found persuasive.

Applicants argue mainly that the McElligott reference does not provide any incentive, motivation or guidance for overcoming the Russell-Jones disincentive for

omitting a carrier molecule from the microsphere. Additionally, Applicants argue that one following the techniques of McElligott would believe that a delivery agent or promoting material for facilitating intracedllular delivery would have be to covalently conjugated to the nucleic acid, which Applicants have shown is not the case.

Applicants' arguments are respectfully found unpersuasive for essentially the same reasons given in the Response for the rejection of 1, 4-6, 13-19, 23-26, 28, 30-31, 33-39 and 48 above. Furthermore, with respect to the second argument it is noted that the claims do not limit that the delivery agent is not covalently conjugated to the nucleic acid.

Conclusions

No claims are allowed.

Claims 8-9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

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